or colpo-microscopy to locate their biopsies, although the work of Grünberger (1951), Grünberger and Antoine (1956), and Navratil *et al.* (1958) makes it clear that these methods greatly enhance the chance of a biopsy including pathological tissue.

Summary

Aspiration cell-smears were compared with scrape tests and a limited series of cervical biopsies in their ability to reveal the presence of carcinoma-in-situ proved by biopsy. The most effective method is the Ayre scrape-smear, which can be used alone since there is no overlap with either the aspiration technique or biopsy.

We acknowledge the assistance in this study given by our clinical colleagues, M. J. D. Noble and J. B. Comerford. We also wish to acknowledge financial support from the British Empire Cancer Campaign.

REFERENCES

Ayre, J. E. (1947). *Amer. J. Obstet. Gynec.*, **53**, 609.
Ericson, C. C., *et al.* (1956). *J. Amer. med. Ass.*, **162**, 167.
Fidler, H. K., Boyes, D. A., and Lock, D. R. (1957). *J. Canad. med. Ass.*, **77**, 79.
Foote, F. W., and Stewart, F. W. (1948). *Cancer*, **1**, 431.
Galvin, G. A., Jones, H. W., and Te Linde (1955). *Amer. J. Obstet. Gynec.*, **70**, 808.
Grünberger, V. (1951). *Acta gynaec. obstet.*, **1**, 208.
—— and Antoine, T. (1956). *Atlas der Kolpomikroscopie.* Thieme, Stuttgart.
Hinselman, H. (1925). *Münch. med. Wschr.*, **2**, 1733.
McLaren, H. C. (1952). *Brit. med. J.*, **1**, 347.
—— (1960). *Acta Un. int. Cancr.*, **16**, 385.
—— Taylor, C. W., and Attwood, M. E. (1956). *J. Obstet. Gynaec. Brit. Emp.*, **63**, 801.
—— —— —— (1958). *Lancet*, **1**, 398.
McLennan, H. R. (1958). Discussion on Cytology, B.M.A. Glasgow Division.
Navratil, E., Bajardi, F., and Nash, W. (1958). *Amer. J. Obstet. Gynec.*, **75**, 1292.
Noble, M. J. D., and Attwood, M. E. (1958). *J. Obstet. Gynaec. Brit. Emp.*, **65**, 64.
Papanicolaou, G. N., and Traut, H. F. (1943). *Diagnosis of Uterine Cancer.* Commonwealth Fund, New York.
Schiller, W. (1928). *Zbl. Gynäk.*, **52**, 1886.
—— (1938). *Surg. Gynec. Obstet.*, **66**, 129.
Scott, Agnes (1960). *J. Obstet. Gynaec. Brit. Emp.*, **67**, 832.
Song, Y. S., Fanger, H., and Murphy, T. (1958). Transactions of Inter-Society Cytology Council, Statler Hotel, N.Y.C., Nov. 13, 1958.
Younge, P. A., Hertig, A. T., and Armstrong, D. (1949). *Amer. J. Obstet. Gynec.*, **58**, 867.
—— and Kevorkian, A. Y. (1959). *Cancer of the Cervix*, Ciba Foundation Study Group 3. Churchill, London.

The importance of diagnosing impaired hearing in young children at as early an age as possible so that the appropriate medical and educational measures can be instituted has been emphasized in guidance issued jointly by the Ministries of Health and Education to local health and education authorities, hospital authorities, and executive councils. Local authorities are asked to review the adequacy of the methods of finding cases of impaired hearing through their maternity and child welfare and school health services; to consult with local medical committees on arrangements for co-operation with general practitioners to ensure a comprehensive system of early ascertainment; and to examine with hospital authorities and local medical committees the arrangements for babies born in hospital. Children considered to be "at risk" are infants with a family history of deafness, and those known to have been subjected to any adverse pre-natal or perinatal influence; children with congenital abnormalities, multiple handicaps, cerebral palsy, and speech defects; and all retarded children.

ACUTE ALCOHOLIC HEPATITIS

BY

A. GORDON BECKETT, B.M., M.R.C.P.
Late Senior Medical Registrar

A. V. LIVINGSTONE, M.B., M.R.C.P.
Senior Medical Registrar

AND

K. R. HILL, M.D., M.R.C.P.
Professor of Pathology

Royal Free Hospital, London

[WITH SPECIAL PLATE]

"One may drink wine and be nothing the worse for it; on another, wine may have effects so inflammatory as to injure him both in body and mind."—SAMUEL JOHNSON (1776).

Severe jaundice is regarded as an ominous event, indicative of impending death, in the chronic alcoholic patient with cirrhosis. Thus in a series of 386 patients with cirrhosis, 65% of whom were jaundiced at some time, Ratnoff and Patek (1942) found that half of the 168 who died jaundiced did so within two months and 85% within a year of the onset of jaundice: and among the alcoholic cirrhotic patients of Boston reported by Summerskill and his colleagues (1960) 11 out of 18 were deeply jaundiced at death and only 4 out of 35 recovered from severe jaundice.

Severe jaundice may, however, occur in alcoholics at an earlier stage, and before cirrhosis is established, when it is accompanied by marked constitutional disturbances —fever, anorexia, abdominal pain, nausea, and vomiting. The liver is enlarged and tender, and shows histologically acute inflammatory changes in addition to those of any underlying condition. The illness tends to run a protracted course, often ends fatally, but is potentially recoverable with suitable treatment.

Jaundice has long been known to follow alcoholic excesses (French, 1912; Hurst, 1934, 1938, 1941; Bocca, 1936), and earlier writers attributed some cases of "acute necrosis of the liver" to an excess of alcohol (Osler, 1892; Rolleston and McNee, 1929). Few other reports of severe jaundice in alcoholics (Davis and Culpepper, 1948; Welin, 1950; Eckhardt *et al.*, 1950) appeared before the importance of acute hepatic insufficiency in chronic alcoholics was stressed by Phillips and Davidson (1954), all of whose 56 patients had drunk heavily before the jaundice developed. These authors assigned a bad prognosis to the condition, many of their patients dying and the remainder showing varying degrees of slow and mainly incomplete recovery. They described a histological picture which they believed to be characteristic and which will be described later. Of 28 patients with the characteristic lesions, 18 died, as did 10 of 13 with severe jaundice.

The object of the present paper is to emphasize the recognition and treatment of this condition, which have received scant attention in the literature of Great Britain. Seven cases of acute alcoholic hepatitis investigated by the authors at the Royal Free Hospital since 1953 are considered, though other such cases were treated in the hospital during that time.

Clinical and Pathological Findings

One case is reported in full below, while the remainder are summarized in Tables I–III.

Case 5

A brewer's drayman aged 45 was first admitted to hospital in September, 1958, with a spontaneous pneumothorax, when the liver was enlarged 4 cm. below the costal margin, but not tender. For about two years he had had a poor appetite, which became worse in the previous two months. He had lost about 1½ stones (9.525 kg.) in weight in four years. Some days he ate no food at all, but drank 6 or 7 pints (3.5 or 4 l.) of beer. At times he had cramps in his legs at night, and these he associated with periods of excessive drinking. For two years he had noticed tremors of the hands. Results of liver-function tests were within normal limits, though the serum albumin level was 3.3 mg. per 100 ml.

He was readmitted to hospital six months later because of jaundice, the duration of which was uncertain. It had undoubtedly been present for three months, during which time the urine had been dark, though the stools had become pale only shortly before admission. There had been marked anorexia for two months, but no nausea or abdominal pain. He denied alcoholism, but later said he had drunk 10 pints (5.68 l.) of beer daily for years and that he had changed to gin after the first admission to hospital. He was unkempt, apathetic, and clinically anaemic; the temperature was 100° F. (37.8° C.); he was thin, jaundiced, and showed a fine non-flapping tremor of the outstretched hands; there was slight palmar erythema; spider naevi were present on the cheeks; the liver edge was tender and palpable 8 cm. below the costal margin.

Investigations.—Results of laboratory investigations are shown in Table IV. On the seventh day the mean cell volume was 120 c.μ, the mean cell haemoglobin concentration 27.7%, and the colour index 1.12. The serum iron level was 180 μg. per 100 ml.

Progress.—Treatment was started with a high-carbohydrate, low-protein, low-fat diet and large dose of aneurin parenterally. Slight lessening of jaundice and improvement in the biochemical findings ensued, but the fever (99°–100° F.; 37.2°–37.8° C.) and jaundice persisted. A superior vena caval drip of 50% glucose solution was started on the 12th day after admission. Three days later jaundice was fading and in a week the temperature subsided to normal, and by

TABLE I.—*Relevant History and Symptoms*

Case No.	Age and Sex	Duration of Acute Illness (Before Admission) (Days)	Duration of Anorexia	Duration of Chronic Alcoholism and Main Drink	Epigastric Pain	Previous Attacks of Jaundice	Known Duration of Fever in Hospital (Days)	Presence of Nausea and Vomiting	Total Time in Hospital (Days)
1	38 F	21	2 years (intermittent)	2 years; spirits	Severe	"Infective hepatitis" 4 years before	14	Yes	13
2	48 M	4	10 days	12 years; spirits	Absent	× 3 after drinking bouts in last 3 years	21	,,	21 (self-discharged)
3	39 M	14	14 ,,	2 years; spirits	Severe	"Infective hepatitis" 10 years before	35	,,	112
4	40 M	5	1 year (intermittent)	1 year; spirits	,,	"Infective hepatitis" 15 years before	28	,,	68
5	45 M	14	2 years (intermittent)	5 years; beer, latterly spirits	Absent	None	21	No	50
6	49 M	28	28 days	10 years; beer and spirits	Severe	,,	28	Yes	28 (self-discharged)
7	55 F	7	35 ,,	20 years; spirits	,,	,,	14	,,	36

TABLE II.—*Main Clinical and Biochemical Features*

Case No.	Liver Enlargement (cm. below R. Costal Margin)	Spleen	Spider Naevi	Palmar Erythema	Signs of Vitamin-B Deficiency	Ascites	Oedema of Ankles	Max. Serum Bilirubin (mg./100 ml.)	Serum Albumin (Lowest Figure) (g./100 ml.)	Prothrombin Concentration (%)	Serum G.O.T. in First Week	Highest Alkaline Phosphatase (K.A. Units/100 ml.)	Highest Neutrophil Count in 1st Week (per c.mm.)	Cerebral State
1	4 cm.; tender	0	0	0	0	+	+	4·2	2·2	—	—	26·0		Delirium
2	8 cm.; tender	+ 2 cm.	0	0	0	0	+	2·0	3·7	—	—	29·5		,,
3	7 cm.; tender	0	0	0	0	0	+	19·0	2·6	41	—	25·0	12,000	,,
4	6 cm.; tender	0	0	0	Cerebral beriberi	0	0	10·0	2·7	43	96	20·0	3,500	Wernicke's encephalopathy
5	8 cm.; tender	0	+	+	0	0	+	8·0	2·4	60	135	27·0	14,250	Confusion
6	12 cm.; tender	+ 2 cm.	+	+	0	+	+	22·0	3·1	42	20	17·0	8,800	Normal
7	6 cm.; tender	0	+	+	0	0	0	8·5	3·4	60	168	39·0	3,500	Confusion

TABLE III.—*Summary of Histological Findings*

Case No.	Type of Specimen	Phase during which Examined	Cirrhosis	Portal Scarring	Fat	Mallory's Hyaline	Cellular Degeneration and Necrosis	Bile Stasis	Acute Inflammation	Bile-duct Hyperplasia
1	Biopsy	Acute	+	+	+	+	+	+	+	+
	P.M.	After treatment	+	+	±	+	0	0	0	0
2	,,	,, ,,	+	+	+	0	0	0	0	±
3	None									
4	Biopsy	Acute	+	+	+	0	+	+	+	+
5	,,	,,	0	+	+	0	+	+	+	+
	,,	After treatment	0	+	±	0	0	0	0	0
6	,,	Acute	+	+	+	+	+	+	+	+
	,,	After treatment	+	+	±	0	0	0	0	0
7	,,	Acute	0	+	+	0	+	+	+	±

TABLE IV

Investigation	Week of Admission					
	1	2	3	4	6–7	12+
Total serum bilirubin (mg./100 ml.)	8·0	2·4		1·8	0·2	0·7
Serum albumin (g./100 ml.)	2·6	2·4	3·1	2·8	4·1	3·9
,, globulin (g./100 ml.)	2·7	2·8	3·4	3·4	3·0	2·9
Thymol turbidity (K.A. units/100 ml.)	1			2		3
Serum alkaline phosphatase (units/100 ml.)	27	14	11	10	14	11
Prothrombin concentration (%)	60	60	60	100	100	
Serum glutamic–oxalacetic transaminase (units/100 ml.)	135	49	28			20
Blood urea (mg./100 ml.)	24	12	28	13	17	
Total W.B.C. (per c.mm.)	11,200	17,600	11,700	12,800	12,100	
Neutrophils (per c.mm.)	8,288	14,250	7,956	8,700	7 190	
Hb (g./100 ml.)	8·3	8·3	14·2	14·8	15·1	16·3
Hb percentage	57	57	97	101	108	112

the 21st day he was well enough to be allowed up. The anaemia (Hb 8.3 g. per 100 ml., with macrocytosis) was corrected by blood transfusions. He was discharged after seven weeks in hospital.

After ten weeks biochemical tests showed great improvement, as did the histology of the second biopsy.

When last seen, in July, 1959, the patient was well and gaining weight, but was drinking again despite warning of the consequences.

Histology.—The first biopsy ten days after admission showed a portal fibrosis with no marked change in the liver architecture and with moderate fatty change. The liver cells showed no Mallory's "alcoholic hyaline" reticulum, but contained glycogen as well as fat. Intralobularly there were many foci of degenerate cells, often infiltrated with leucocytes, which were mainly polymorphonuclears, but mononuclears and eosinophils were also present; in some areas whole lobules appeared to be degenerating, simulating the appearances of massive necrosis. Bile stasis and thrombi were very prominent. The portal triads showed stellate scarring and marked bile duct hyperplasia, and were heavily infiltrated with leucocytes of all types; they were oedematous.

The second specimen, taken about three months later, showed considerable improvement; the fat had almost disappeared, as had the acute inflammatory cellular infiltration. The disappearance of the fat was associated with increase in cytoplasmic granules and a very mild bile stasis (no thrombi). There was no evidence of hepatocellular degeneration or necrosis, but there was increase in cellular polyploidy. The triads showed residual scarring, but no acute inflammatory changes. Reticulin stains showed an apparent increase and consolidation of the fibrosis, but this was due to the collapse of a reticulin network formerly distended by swollen cells and to inflammatory oedema.

In summary, the biopsy after three months' treatment revealed a loss of fat, bile stasis, and hepatocellular degeneration, with disappearance of the acute inflammatory reaction, leaving some residual scarring of the portal tracts.

Summary of the Histological Appearances of Seven Cases

Basically, there appears generally to be evidence of previous damage extending from a mild chronic inflammation and stellate scarring of the portal tracts, with no disorganization of architecture, to a frank cirrhosis with nodular hyperplasia. Superimposed upon these chronic changes of pre-cirrhosis and cirrhosis there is evidence, in the acute exacerbations, of focal (Special Plate, Fig. 1) and massive cellular degeneration and necrosis, marked fatty change and bile stasis (Special Plate, Fig. 2), and a reactive bile-duct hyperplasia with an acute inflammatory reaction (Special Plate, Fig. 3)—the so-called alcoholic hepatitis. These acute changes may disappear after treatment (Special Plate, Fig. 4).

Mallory's "alcoholic hyaline" reticulum was not an invariable finding in these cases of alcoholism, only two cases showing the lesion. In one patient who recovered the hyaline reticulum appeared to have disappeared completely; in another, though the acute inflammatory reaction had disappeared, as had most of the fat, the presence of the hyaline reticulum in the cells had increased in amount at the time of death.

Discussion

Commentary on the Seven Cases

The more constant features of this illness need emphasis, as it may be mistaken for infective hepatitis or for surgical jaundice, even when cirrhosis is known to be present. Six of the patients were from the professional middle class, a fact in keeping with the cost of alcoholic drinks in Britain. Only one of our patients admitted not eating enough food; he was a brewer's drayman (Case 5) who, unable to afford both, lived increasingly on alcohol. Welin (1950) noted the same social and dietary aspects in Scandinavia. In America the majority of similar cases described come from the ranks of unemployed, unskilled or semi-skilled, who commonly are observed to have nutritional deficiencies (Summerskill *et al.*, 1960). All our patients had increased their drinking excessively just before their illness; three patients, returning from overseas, reported increased consumption of alcohol at farewell celebrations immediately preceding the onset of jaundice, and a fourth drank more heavily than usual over Christmas. The patient in Case 2, the only true dipsomaniac of the group, had precipitated several attacks of jaundice by his debauches. All the patients were long-standing drinkers of spirits (regularly one bottle of spirits and often much more daily), except Case 5, and his illness coincided with a change from beer to gin. The condition also may develop in beer-drinkers (Ratnoff and Patek, 1942; Summerskill *et al.*, 1960).

Some scepticism is advisable in accepting personal accounts of alcoholic intake of these patients—for example, because of mental impairment at some stage of the illness (Cases 1–5 and 7), and also because social as well as clinical accounts of alcoholic consumption tend to err greatly to the side of understatement (Welin, 1950; Klatskin, 1959). It is unlikely that any really accurate records of the consumption of food and drink by the alcoholic have yet been obtained. The majority of these patients did not volunteer information about the amount of alcohol they drank, and three in this series, when first asked specifically about it, denied that they did so at all. Similar experiences are reported by Welin (1950) and, particularly in women, by Summerskill *et al.* (1960).

Four patients had had previous single attacks of jaundice, diagnosed as "infective hepatitis," from 4 to 16 years before the illness described here. Though only one was known to be actively alcoholic at the time of the first attack of jaundice, three others were probably already heavy drinkers. In published series antecedent jaundice in such cases is comparatively rare.

The onset of the illness was acute in four cases, but more insidious in the others. Jaundice had been noted for a week or less before admission in four, and from three weeks to four months in the others.

The outstanding single symptom of these patients was anorexia, which preceded the jaundice in each by a widely varying interval, and may have marked the onset of liver dysfunction irrespective of when the jaundice subsequently occurred. At some stage in all these cases it became so severe as to induce total abstinence—an important feature of successful treatment. Persistent epigastric pain was a striking feature in three cases, and was only partially relieved even with strong analgesics. With anorexia four had severe nausea and vomiting. Liver enlargement and hyperaemia of the stomach were presumably responsible for these symptoms, though they may have been early manifestations of Wernicke's encephalopathy.

As in other series (for example, Phillips and Davidson, 1954 ; Summerskill *et al.*, 1960) this illness was invariably accompanied by fever, sometimes high ; here in all cases the fever lasted at least two weeks after admission, and in five it persisted for up to four weeks. This contrasts with the temperature pattern usual in infective hepatitis, where the temperature commonly falls with the appearance of the jaundice.

All these patients had a tender liver, enlarged in varying degrees ; in one case (No. 6) it was palpable well below the umbilicus. Only in two cases was the spleen palpable ; two had ascites and oedema, and three had some of the stigmata of chronic liver disease.

Though vitamin-B deficiency has been widely implicated as an aetiological factor in cirrhosis in this series, only one patient showed clinical evidence of vitamin-B deficiency on admission ; but the precipitation of Wernicke's encephalopathy in Case 4, and possibly in Case 3, by diarrhoea, high-carbohydrate diet, and inadequate vitamin-B therapy suggested a latent deficiency in these patients.

Mental impairment, varying from apathy, inattention, and depression to frank delirium, occurred at some stage in six patients ; in three the response to aneurin indicated deficiency of this vitamin to be the underlying cause.

Laboratory investigations, usually valuable as diagnostic aids in jaundiced patients, were only of limited or negative value in the present series, in the last five cases of which they were most comprehensively carried out. The so-called " liver-function test " suggested liver-cell damage with some intrahepatic obstruction rather than a primarily extrahepatic type of jaundice, but in the most severely ill patient (Case 3) the tests for hepatocellular degeneration never gave strikingly abnormal results. There were high serum bilirubin values in Cases 3 and 6 (19 and 22.5 mg. per 100 ml. respectively), in both of which recovery took place. A low serum albumin level was found at some stage in Cases 1, 2, and 5 ; though this is generally regarded as a poor prognostic feature, one of these patients made a virtually full clinical and pathological recovery. The serum glutamic–oxalacetic transaminase level was raised in three out of four cases, and fell to normal with clinical recovery from the acute stage ; in the fourth case it was not significantly raised when a severe degree of clinical and biochemical liver damage existed. The prothrombin concentration was greatly diminished in five cases, and, as anticipated, did not alter with parenteral administration of vitamin K. Welin (1950) and Eckhardt *et al.* (1950) have likewise suggested that liver-function tests may be of no positive diagnostic value in such cases. According to Ducci (1957), alcoholic cirrhosis with jaundice bears no biochemical resemblance to acute viral hepatitis ; in the former he found the enzymes normal or only slightly raised, the thymol turbidity slightly increased, and the thymol flocculation generally negative, and concluded that the jaundice in alcoholic cirrhosis is not due to a virus, but is a grave complication of the disease.

In contrast, the leucocyte count is considered to be a valuable diagnostic aid. Thus, Phillips and Davidson (1954) and Summerskill *et al.* (1960) found a neutrophil leucocytosis in the peripheral blood of all patients whose serum bilirubin was above 5 mg. per 100 ml., and the former considered it to indicate a bad prognosis. This was not so in our series, in which a neutrophil leucocytosis was present in four cases, though the very high values reported by Phillips and Davidson were not seen. A neutrophil leucocytosis, when present, is of undoubted importance in distinguishing this condition from infective hepatitis and some other types of jaundice.

Anaemia is a feature of some of these cases. Anaemia or a fall in haemoglobin concentration occurred at some stage in six cases of the present series, three of which had macrocytosis and one reticulocytosis. The pathogenesis was not fully understood, but was probably haemolytic, at least in part when haemodilution or gastro-intestinal haemorrhage, liable to be present in such cases, could be excluded. Such an anaemia is known to occur in some patients with cirrhosis without severe jaundice, as described by Jandl (1955), who demonstrated an increased rate of red-cell destruction, probably due to excessive splenic activity, in all his patients with cirrhosis, while a small proportion had severe anaemia with evidence of folic-acid deficiency. He also found a reticulocyte peak about seven days after withdrawal of alcohol, and concluded that alcohol directly or indirectly had a toxic action on the bone-marrow. Writing on a " new symptom complex," Zieve (1958) reported five alcoholic patients with acute jaundice, a transient haemolytic anaemia arising in the early stages, and hypercholesterolaemia, though the serum cholesterol of four of our patients with anaemia remained within the normal range. Froehlich (1958) had described hyperlipaemia, mainly of neutral fat, but also with a high serum cholesterol level, in acute alcoholism without jaundice.

In general, the abnormality of the biochemical values did not seem to be of direct prognostic significance, and neither did the clinical estimate of the gravity of the patient's condition. Whether this would have been so bad had the treatment been different remains an interesting but profitless speculation.

The lack of awareness of the condition of acute alcoholic hepatitis in Great Britain and the absence of diagnostic laboratory tests obviously create a danger of misdiagnosis and hence inappropriate treatment. The duration and depth of the jaundice might easily lead to surgical advice being sought primarily, especially when the jaundice is associated with upper abdominal pain and vomiting. This happened in Case 1 ; the laparotomy with drainage of ascites probably removed whatever chances of recovery the patient had. In all, three of these patients were admitted originally to surgical wards, and surgical opinion was sought early in Case 3.

Needle biopsy of the liver, with the usual precautions, seems at present to be the most valuable method of differentiating between this type of jaundice and other forms ; the histology is discussed later.

Treatment

Initial treatment should begin without delay and must depend on awareness of the condition and its early diagnosis. It is based on the removal of the presumed toxic factor, alcohol, together with rest in bed and the use of a high-calorie diet. Because of anorexia, nausea, and vomiting many of these patients may be quite unable to take the required 3,000 calories by mouth, and parenteral fluids then become obligatory. Hypertonic glucose (50%) by vena-caval drip, which can be maintained for long periods, appears to be the method of choice, and the institution of this form of therapy marked the turning-point in Cases 3, 4, and 5.

However, some improvement may take place even on a poor diet after cessation of alcoholic intake (Eckhardt *et al.*, 1950), as occurred in Cases 2 and 5. Davidson (1958) claims that normal diet is adequate for recovery, but most nauseated patients have difficulty in taking this orally.

Though most of these patients are able to metabolize moderate amounts of protein, many workers have pointed out serious consequences (liver coma, neuropsychiatric abnormalities, etc.) of high-protein diets in the presence of liver failure and porto-caval shunts (Walshe, 1951; Riddell and McDermott, 1954; Sherlock *et al.*, 1954; Summerskill *et al.*, 1956). It seems rational, therefore, to restrict protein intake, in severe cases at least, until some degree of recovery has taken place. Subsequently a high protein intake is desirable; Eckhardt and his colleagues (1950) found that this type of patient improved only to a certain point until protein was added to the diet. The emphasis on carbohydrate therapy and the theoretical probability of pre-existing vitamin deficiencies imply that vitamin B in large doses is an important adjunct; the need for this is illustrated by the occurrence of Wernicke's encephalopathy in Case 4 and probably in Case 3.

If there is evidence of portal hypertension or gastro-intestinal haemorrhage, gut sterilization by wide-spectrum antibiotics is advisable to reduce absorption of bacterial protein and perhaps to suppress the formation of other as yet unidentified products of bacterial action.

Whatever part alcohol plays in the production of the acute condition under discussion, most authorities on cirrhosis tacitly, if not openly, admit its major role by agreeing on the need for subsequent total abstinence by patients under their care, and, though recovery from the acute illness may be complete, this only marks the beginning of a long-continued supervision, wherein advice often goes unheeded and cirrhosis develops and progresses inevitably to death.

Histology

In our series the histological lesion appears to be an acute hepatocellular degeneration and fatty change proceeding to a patchy necrosis; the latter tends to evoke an acute inflammatory reaction. Both the degenerative condition and the inflammation subside after suitable treatment.

Similar findings were recorded by Davis and Culpepper (1948) in one patient studied by serial biopsies. Phillips and Davidson (1954) drew attention to the acute phase in chronic alcoholism; the changes described appear to be essentially similar to those of our series, but they went further, as they felt that they could relate the degree of inflammatory cellular reaction to the severity of the illness. Gall (1957) also found similar morphological changes in acute alcoholism which he named "toxic hepatitis." Many workers are agreed that the fatty change in the acute phase of alcoholism is indicative of hepatocellular degeneration, which may be reversible after treatment (Davis and Culpepper, 1948; Phillips and Davidson, 1954; Gall, 1957; Popper and Szanto, 1957).

There is, however, no unanimity of opinion concerning the significance of the presence of the so-called "alcoholic hyaline" reticulum regarded by F. B. Mallory (1911) as specific. Popper (1959) and Summerskill *et al.* (1960) have not seen it in non-alcoholics, whereas Baggenstoss and Stauffer (1952) have found it in post-hepatitic cirrhosis, and Steiner (1959) claims to have found it in non-alcoholics in Africa.

According to G. K. Mallory (1960), the thesis that all cells containing hyaline reticulum become necrotic is much disputed, but there is considerable evidence that the condition may be reversible. The evidence in our hands is in keeping with this statement: in Case 1 the hyaline increased after treatment despite concurrent loss of fat, and in Case 6 it disappeared.

The histological diagnosis of adequate specimens of liver obtained by needle biopsy presents little difficulty. In viral hepatitis the zonal distribution contrasts with the patchy cellular necrosis of alcoholism, and consideration of the clinical and biochemical findings will help in making a further distinction between the two. Though it has often been postulated that the two conditions may be superimposed, Popper (1957) is of the opinion that in practice the histological indications that the two have coexisted have not been recorded in the literature.

Differentiation from intrahepatic and drug-induced jaundice should prove of no difficulty, because of the absence of fatty change in these conditions.

Case 1 showed a chronic pancreatitis at necropsy; this is in keeping with the views of Shallenberger and Kapp (1958), who claimed that of all cases of pancreatitis 20% are associated with alcoholism, and of Owens and Howard (1958), who found that all the patients with pancreatic calcification seen in the Grady Memorial Hospital, Atlanta, Georgia, were advanced alcoholics. On the other hand, Pollock (1959) in Great Britain did not consider that alcoholism had any part to play in his series of cases of pancreatitis.

Aetiology

Excluding intercurrent conditions of separate aetiology, such as reactions to drugs, jaundice may develop in alcoholics in several ways: (1) as in the cases described, following excessive drinking; (2) after gastro-intestinal haemorrhage, when anoxia of a damaged liver and the increased metabolic work in dealing with the sudden increase in protein absorption appear to be responsible; and (3) as a terminal event in advanced and already irreversible liver-cell failure (often associated with gastro-intestinal haemorrhage). The last two occur at an advanced stage of cirrhosis, whereas the first may occur at any time. Minor degrees of jaundice also occur, apparently unrelated to excessive intake of alcohol in the so-called active phase of cirrhosis. A relationship between active cirrhosis and the illness described in this paper has not been estab-

lished, chiefly because of lack of reliable information concerning drinking habits. It is also not certain whether the attacks of hepatitis described here represent stages in the development of cirrhosis, or whether, with subsequent abstinence, any liver damage which has already occurred remains stationary or even resolves. Our study suggests the latter is true, though the period of follow-up is relatively short. As several of these patients were said to have had "infective hepatitis" many years previously, it is conceivable that alcohol might have reactivated the infection; a further possible explanation which has been suggested is that the illness was a primary viral hepatitis developing in a liver already damaged and cirrhotic. This is contrary to the different histological and biochemical pictures and goes against clinical experience (Popper, 1957).

Despite the long-accepted association between alcoholism, a fatty liver ("pre-cirrhosis"), and cirrhosis, no conclusive evidence exists to show that alcohol is directly responsible, and other mechanisms, such as malnutrition and vitamin-B deficiency, have been blamed. The chief difficulties in establishing such a relationship lie in the failure to produce cirrhosis regularly in animal experiments by giving alcohol, and in the relatively small proportion of human alcoholics who develop cirrhosis, estimated to be about 8% in the United States.

The fatty liver of alcoholics is usually considered to be a pre-cirrhotic condition, and its potential reversibility has been stressed (Connor, 1938; Hall and Morgan, 1939; Welin, 1950; Popper and Szanto, 1957; Klatskin, 1959), though this has been denied (Dible, 1951). Fatty infiltration of the liver was demonstrated by Ashworth (1947) to follow the ingestion of alcohol by rats in spite of adequate diet, while improvement has been observed to follow the withdrawal of alcohol (Klatskin and Yesner, 1949).

The severe illness described here seems to be more closely related to the direct toxic action of alcohol on the liver than with malnutrition. It followed closely upon alcoholic debauches, and, though the exact intake of food on these occasions is not known, most of our patients appeared to eat normally until the onset of anorexia. On the other hand, if alcohol is finally utilized as a carbohydrate, the two sharing a common pathway from the pyruvate stage, then clearly a relative excess of carbohydrate over protein existed. But if this is an aetiological factor, and an absolute excess of carbohydrate over protein has been held responsible for liver damage, it is paradoxical that a pure carbohydrate diet of 3,000 calories should have caused improvement. Similarly, it is difficult to involve aneurin deficiency, as in one case the hepatic condition improved on a regimen which itself produced cerebral beriberi. We have unpublished evidence that subicteric attacks of hepatitis may be produced by excessive drinking, and it is suggested that cirrhosis in the alcoholic may be caused by repeated minor attacks of hepatitis, clinical or subclinical, icteric or non-icteric, produced by the direct toxic action of alcohol.

Other descriptions have been used for this condition. Phillips and Davidson (1954) called it "acute hepatic insufficiency of chronic alcoholics," but they also included in this category what appears to be the terminal phase of cirrhosis, when the production of jaundice and of hepatic insufficiency is almost certainly different from that of the acute and potentially reversible stage. More recently the Boston group of workers (Davidson, 1958) have used the term "active cirrhosis" for at least some of these cases; this term implies that the cause of the acute illness and that of cirrhosis are the same. At present it is by no means certain that this is so; in addition there is no doubt that the acute condition may occur in the absence of cirrhosis.

The term "acute alcoholic hepatitis" was used by Hurst (1934, 1938) for a pre-cirrhotic state, sometimes accompanied by slight jaundice, in which complete histological recovery followed total abstinence, but he also applied it to patients the description of whose condition suggested a chronic hangover and who were never jaundiced at all. Moreover, these patients were mainly young adults, in contrast to the older age of patients of the present and similar series. Cases histologically resembling the present ones were described by Gall (1957) as "toxic hepatitis," but the term lacks specificity and indeed urgency.

The term which we prefer is "acute alcoholic hepatitis." The word "hepatitis" is not entirely satisfactory, as some of the histological changes are degenerative (as they may be in any form of inflammation) and may possibly arise from a deficiency state. On the other hand, the classic changes of acute inflammation are present, though presumably induced chemically rather than by bacteria or viruses. This name gives the impression of an acute condition which, as there seems to be no reliable prognostic guide to the eventual outcome, merits urgent and energetic treatment.

Summary

Acute alcoholic hepatitis often follows intensified drinking, usually by the chronic alcoholic, and is characterized by jaundice, which is often severe, anorexia, nausea, vomiting, upper abdominal pain, hepatomegaly, and fever. Details of seven cases are presented.

The illness described may be readily misdiagnosed as infective hepatitis or surgical jaundice even when cirrhosis is known to be present and treatment wrongly planned.

In the cases reported biochemical investigations did not show any characteristic pattern, though they suggested liver-cell damage with an additional obstructive element to the jaundice. In severe cases a neutrophil leucocytosis is present. Anaemia, possibly haemolytic in origin, commonly develops.

Histologically, there is evidence of focal and massive cellular degeneration and necrosis, marked fatty change, bile stasis, and a reactive bile duct hyperplasia with an acute inflammatory reaction. Mallory's alcoholic hyaline reticulum is not invariably present. These acute changes, which disappear after treatment, are superimposed on existing changes of pre-cirrhosis or cirrhosis.

Treatment consists of withdrawal of alcohol, rest in bed, a high calorie intake (by vena-caval drip if necessary), and large supplements of vitamin B. In the earlier stages reduction of protein intake is theoretically desirable, and with such treatment the reported high fatality rate may be lowered and liver function in some cases restored to normal. With recovery, however, the main problem, that of preventing continued alcoholism, remains.

We wish to thank Dr. Una Ledingham, who was at some stage responsible for the clinical management of six patients,

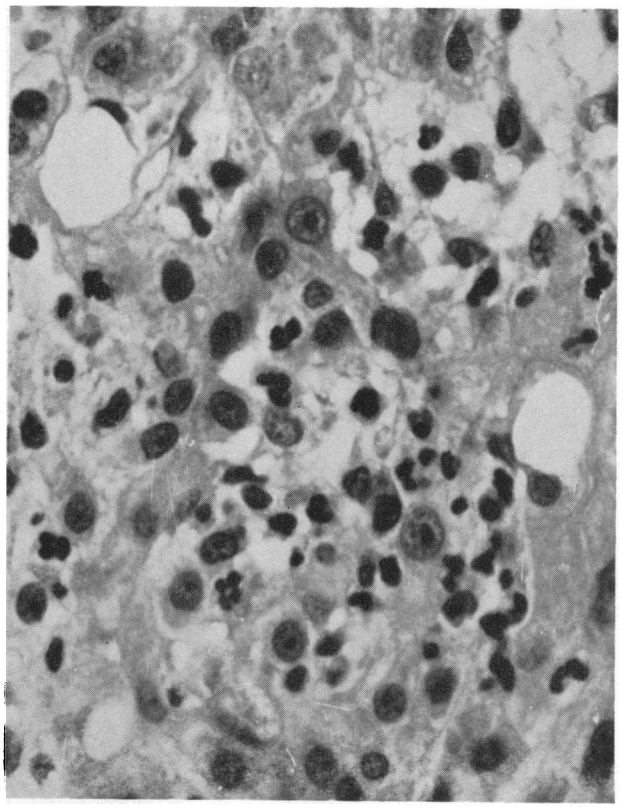

Fig. 1.—Acute alcoholic hepatitis. Focal area of cellular degeneration infiltrated with polymorphonuclear leucocytes. (H. and E. ×160.)

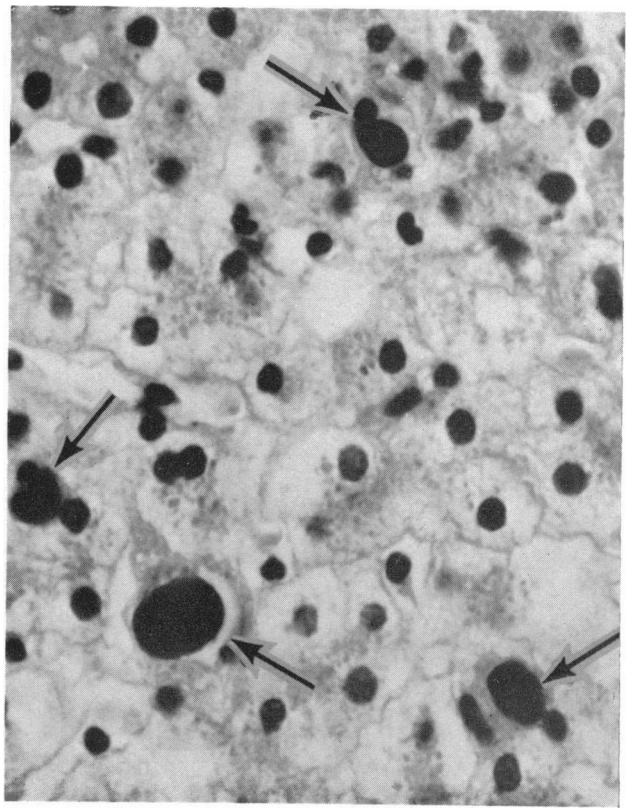

Fig. 2.—Acute alcoholic hepatitis. Bile thrombi indicated by arrows. There are considerable cellular degeneration and much granular pigment (bile stasis). (H. and E. ×160.)

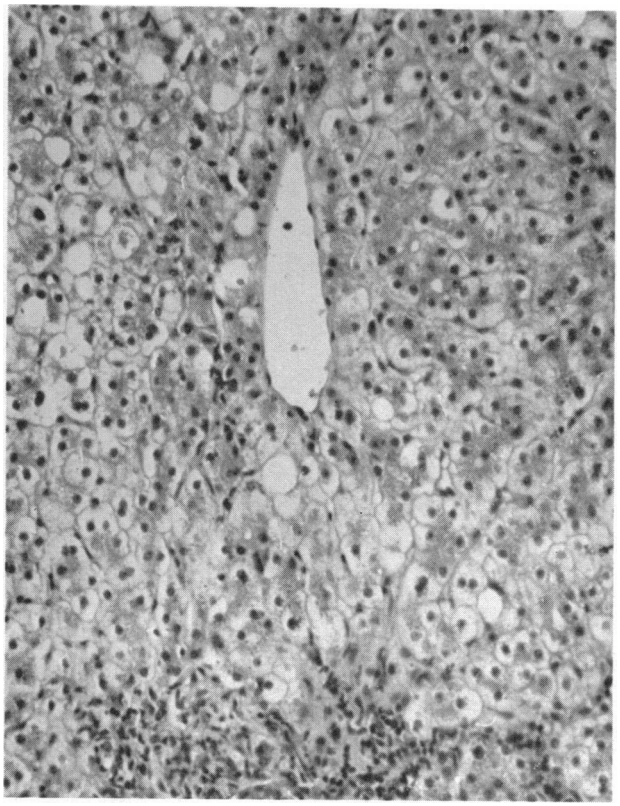

Fig. 3.—Acute alcoholic hepatitis. The cells are vacuolated and there are acute inflammatory exudates both intralobularly and portally. (H. and E. ×40.)

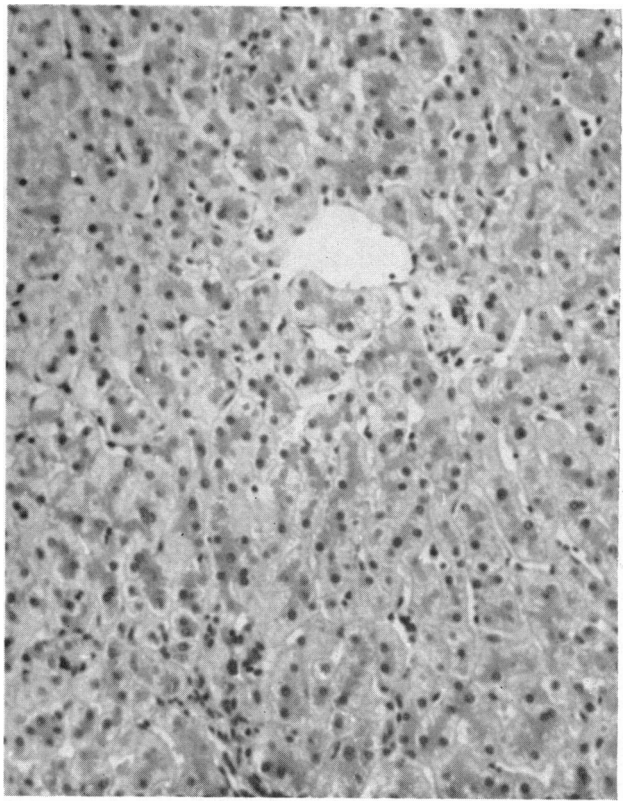

Fig. 4.—Acute alcoholic hepatitis following recovery. The same case as in Fig. 3 but 12 weeks later. Note that the inflammatory reaction has subsided and the cells are no longer vacuolated. (H. and E. ×40.)

for her help and encouragement to make this study; Professor Sheila Sherlock for permission to study Case 7, Dr. A. M. Ramsay for Case 3, and Mr. George Qvist for Case 6. For their willing help in the secretarial work involved we must thank Miss H. M. Haestier and Miss P. C. Wraight.

REFERENCES

Ashworth, C. T. (1947). *Proc. Soc. exp. Biol. (N.Y.)*, **66**, 382.
Baggenstoss, A. H., and Stauffer, M. H. (1952). *Gastroenterology*, **22**, 157.
Bocca, C. R. (1936). *J. Méd. Lyon*, **17**, 701.
Connor, C. L. (1938). *Amer. J. Path.*, **14**, 347.
Davidson, C. S. (1958). *Amer. J. Med.*, **25**, 690.
Davis, W. D., and Culpepper, W. S. (1948). *Ann. intern. Med.*, **29**, 942.
Dible, J. H. (1951). *Brit. med. J.*, **1**, 833.
Ducci, H. (1957). In *Hepatitis Frontiers*, ed. F. W. Hartman, G. A. LoGrippo, J. G. Mateer, and J. Barron. Henry Ford International Symposium, p. 585. Churchill, London.
Eckhardt, R. D., Zamcheck, N., Sidman, R. L., Gabuzda, G. J., and Davidson, C. S. (1950). *J. clin. Invest.*, **29**, 227.
French, H. (1912). *An Index of Differential Diagnosis of Main Symptoms*, p. 368. Wright, Bristol.
Froehlich, A. L. (1958). *Acta gastro-ent. belg.*, **21**, 33.
Gall, E. A. (1957). In *Hepatitis Frontiers*, ed. F. W. Hartman, G. A. LoGrippo, J. G. Mateer, and J. Barron. Henry Ford Hospital International Symposium, p. 475. Churchill, London.
Hall, E. M., and Morgan, W. A. (1939). *Arch. Path.*, **27**, 672.
Hurst, A. F. (1934). *Practitioner*, **133**, 553.
—— (1938). *Brit. med. J.*, **1**, 661.
—— (1941). In *A Textbook of the Practice of Medicine*, ed. F. W. Price, 6th ed., p. 699. Oxford University Press, London.
Jandl, J. H. (1955). *J. clin. Invest.*, **34**, 390.
Johnson, S. (1776). In *Boswell's Life of Johnson*, 1946 ed., vol. 2, p. 39. Oxford.
Klatskin, G. (1959). *J. Amer. med. Ass.*, **170**, 1671.
—— and Yesner, R. (1949). *J. clin. Invest.*, **28**, 723.
Mallory, F. B. (1911). *Johns Hopk. Hosp. Bull.*, **22**, 69.
Mallory, G. K. (1960). *Lab. Invest.*, **9**, 132.
Osler, W. (1892). *The Principles and Practice of Medicine*, p. 444. Young J. Pentland, Edinburgh.
Owens, J. L., jun., and Howard, J. M. (1958). *Ann. Surg.*, **147**, 326.
Phillips, G. B., and Davidson, C. S. (1954). *Arch. intern. Med.*, **94**, 585.
Pollock, A. V. (1959). *Brit. med. J.*, **1**, 6.
Popper, H. (1957). In *Hepatitis Frontiers*, ed. F. W. Hartman, G. A. LoGrippo, J. G. Mateer, and J. Barron. Henry Ford Hospital International Symposium, p. 584. Churchill, London.
—— (1959). *Lancet*, **2**, 1077.
—— and Szanto, P. B. (1957). *J. Mt Sinai Hosp.*, **24**, 1121.
—— —— and Elias, H. (1955). *Gastroenterology*, **28**, 183.
Ratnoff, O. D., and Patek, A. J. (1942). *Medicine (Baltimore)*, **21**, 207.
Riddell, A. G., and McDermott, W. V. (1954). *Lancet*, **1**, 1263.
Rolleston, H. D., and McNee, J. W. (1929). *Diseases of the Liver, Gall-bladder and Bile-ducts*, 3rd ed., p. 616. Macmillan, London.
Shallenberger, P. L., and Kapp, D. F. (1958). *Ann. intern. Med.*, **48**, 1185.
Sherlock, S., Summerskill, W. H. J., White, L. P., and Phear, E. A. (1954). *Lancet*, **2**, 453.
Steiner, P. E. (1959). Ibid., **2**, 1077.
Summerskill, W. H. J., Davidson, C. S., Dible, J. H., Mallory, G. K., Sherlock, S., Turner, M. D., and Wolfe, S. J. (1960). *New Engl. J. Med.*, **262**, 1.
—— Davidson, E. A., Sherlock, S., and Steiner, R. E. (1956). *Quart. J. Med.*, **25**, 245.
Walshe, J. M. (1951). Ibid., **20**, 421.
Welin, G. (1950). *Acta med. scand.*, Supplement, **246**, 260.
Zieve, L. (1958). *Ann. intern. Med.*, **48**, 471.

A bilharziasis eradication project—the first of its kind in the world—is at present under way in Egypt with the assistance of the World Health Organization. The project gained priority because of the fear that the bilharziasis problem will loom larger when the Aswan High Dam is completed seven years from now. The lake that will form behind the dam will be the largest man-made lake in the world, and could become another fertile breeding-place for the parasite-carrying snails. The eradication project will strengthen existing control measures. At present there are 859 bilharziasis treatment centres in Egypt, which made it possible to detect and treat 4,000,000 cases in 1960 as against only 1,000,000 cases in 1952. (WHO/31, July 28.)

DILATATION OF THE COLON IN ULCERATIVE COLITIS

BY

PHILLIDA A. SAMPSON,* M.B., Ch.B.
D.Obst.R.C.O.G.
Research Associate, Department of Surgery

AND

F. C. WALKER,† Ch.M., F.R.C.S., F.R.C.S.Ed.
Lecturer in Surgery
University of Birmingham

[WITH SPECIAL PLATE]

The recognition of dilatation of the colon as a complication of ulcerative colitis has been reported infrequently; the condition can occur either in an acute first attack or in an acute relapse of a chronic ulcerative colitis. Though not mentioned in a review of the local complications in 2,000 cases seen by Sloan *et al.* at the Mayo Clinic in 1950, in 1951 Madison and Bargen reported a case of "unusual segmental dilatation" of the transverse colon without distal obstruction which occurred in a patient with a fulminating relapse of chronic ulcerative colitis of 11 years' duration. The syndrome was referred to in general terms by Brooke (1954) in his monograph, while Lumb *et al.* (1955) reported a series of seven cases, and Roth *et al.* (1959) have drawn further attention to it. The term "toxic dilatation" was used by Marshak and his colleagues (1960), and this has the merit of drawing attention both to the extreme illness of the patient and to the fact that perforation of the colon is imminent.

During the last five years cases of chronic dilatation have been a source of special study in this centre, with particular regard to treatment. During this period 168 patients came to operation for ulcerative colitis; 14 had dilatation. It is our purpose to present the problems encountered in diagnosis, management, and the outcome. The following case reports are representative.

Illustrative Cases

Case 2

A woman secretary aged 41 was admitted in December, 1956, with a six-weeks history of diarrhoea with blood and mucus and a bowel frequency of D=5–6; N=1–2. She was pale and ill, with a deep venous thrombosis in the left leg; her abdomen was distended, the transverse colon being easily palpable, and there were exaggerated bowel sounds which were obstructive in character. The incomplete small-bowel obstruction was treated conservatively and settled. She was given hydrocortisone retention enemata in an attempt to control the colitis, but the abdominal distension increased and eventually a primary colectomy had to be undertaken.

Laboratory investigations showed: haemoglobin 13.1 g. per 100 ml. (88%); serum sodium 130, potassium 3.6, and chloride 95 mEq per litre; serum albumin 1.7 g. and globulin 2.5 g. per 100 ml.; blood urea 22 mg. per 100 ml. A straight radiograph of the abdomen showed marked gaseous distension of the bowel with fluid levels.

At operation the transverse colon was found to be adherent to the peritoneum, and was opened inadvertently in the abdominal incision. There was gross distension of the whole bowel, its wall being paper thin.

*Supported by a grant from the Medical Research Council.
†Now Reader in Surgery, University of Durham.